REMARKS

Claims 1-6 and 8-23 are pending.

Applicants acknowledge with appreciation the Office's withdrawal of the prior rejections under 35 U.S.C. §§ 102, 103, and 112. *See* Office Action at page 2. The Office now rejects the pending claims under 35 U.S.C. § 103. Applicants address these rejections below.

Rejection Under 35 U.S.C. § 103 over Johansen, Jardieu, and Frank

Claims 1-5, 8-16, and 21-23 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent 6,087,188 ("Johansen") in view of U.S. Patent 6,037,453 ("Jardieu") and U.S. Patent 6,060,326 ("Frank"). Office Action at page 3. The Office alleges that Johansen teaches "a method of detecting an antibody in a sample using a labeling compound." Office Action at page 4. According to the Office, Johansen teaches the following steps:

> mixing the ligand antigen, antibody or hapten bound to biotin with the sample; an antibody is directed against the antibody to be detected bound to []paramagnetic particles; and a chemiluminescent acridinium compound bound to avidin or streptavidin to form a solid phase complex; separating the solid phase from the liquid phase; and analyzing the separated solid phase for the presence of chemiluminescent complex.

Id. The Office acknowledges that Johansen "fails to teach using an IgE receptor such as CD23 (FcERII) to bind IgE antibody/ligand complexes." *Id.* at page 5. The Office also recognizes that, with respect to claim 15, Johansen fails to teach that "the IgE is quantified using CD23 alone to obtain a first measurement and using FceRI alone to

obtain a second measurement, and using both first and second measurements as the basis for evaluating the immunological status of the subject." *Id.* at pages 5 and 6.

Regarding Jardieu, this reference allegedly teaches "an assay protocol for IgE antibody variants, which comprises coating the Fc epsilon RI or RII (CD23) receptor on a well plate (carrier)." Office Action at page 6. The Office contends that Jardieu teaches mixing IgE variants and the MaE11 (anti-IgE) antibody with biotinylated IgE to form "mixture I." *Id.* Jardieu then allegedly adds "mixture I" to plate-bound FcεRII to create "mixture II," adds streptavidin-HRP, washes the plate, and then adds "a substrate to the plate for developing a detectable color." *Id.* According to the Office, "[t]he label (streptavidin-HRP) does not associate with the carrier/plate coating the Fc epsilon RII receptor because the streptavidin would bind to the biotinylated IgE (ligand)." *Id.* As discussed below, however, the Office's current interpretation of Jardieu remains incorrect.

With respect to claim 15, the Office states that "Jardieu teaches that FCEH (FceRI) and FcERII (CD23)-specific, differential binding polypeptides are useful for diagnostics and therapeutics" and "method of identifying immunoglobulin analogues that bind FCEH (FceRI) but not FCEL (FceRII- CD23)." *Id.*

Attempting to identify an alleged motivation to combine Johansen and Jardieu, the Office turns to Frank, alleging that Frank teaches "detecting IgE antibodies using an Fc epsilon receptor Fc[ε]R instead of anti-IgE antibodies to avoid cross-reactivity with other antibody idiotypes such as gamma isotype antibodies." *Id.* The Office also contends that Frank "teaches that IgE binds to the Fc epsilon receptor with high[er] affinity than the anti-IgE antibodies (*See* col. 1, line 45-col. 2, line 10)." *Id.*

Applying its understanding of these references, the Office concludes that it would have been obvious to modify Johansen's methods by replacing the anti-IgE antibody with CD23 as allegedly taught in Jardieu. Office Action at page 7. Relying on the alleged teachings of Frank, the Office urges that one would have been motivated to make such a modification "because it is well known that Fc epsilon receptor binds to the IgE with higher affinity and no cross-reactivity with other gamma isotype[] antibodies." *Id.*

With respect to claim 15, the Office contends that, based on Jardieu, it would have been obvious to "evaluate the immunological status of a subject by quantifying the IgE that binds to FCEH [the high affinity Fcε receptor] but not to FCEL [the low affinity Fcε receptor] or IgE that binds to FECL but not FCEH." *Id.* The Office further contends that because "there are certain IgE that binds to FECH but not to FECL and certain IgE that binds to FECL but not to FECH, it would have been obvious . . . to quantify both types of IgE by taking both measurements." *Id.*

Applicants respectfully traverse and discuss each reference to address their combined teachings as a whole. The combination of Johansen, Jardieu, and Frank would not have rendered claims 1-5, 8-16, and 21-23 obvious. As admitted by the Office, Johansen does not teach use of the low affinity FcεR, CD23, in a method of detecting and/or quantifying an IgE antibody. Johansen instead uses anti-IgE antibodies.

The Office's rationale, which relies on Frank, to allegedly support this obviousness rejection teaches away from the claimed invention. Specifically, the Office contends that one would be motivated to modify Johansen with Jardieu "because it is

well known that Fc epsilon receptor binds to the IgE with higher affinity and no cross-reactivity with other gamma isotype[] antibodies." Office Action at page 7. The Office's alleged motivation is based on the belief that a reagent with higher affinity works better. Likewise, Frank teaches that a "canine FcεR molecule provides an advantage over, for example, anti-IgE antibodies, to detect IgE because a canine FcεR molecule can bind to canine IgE with *more specificity (i.e., less idiotype cross-reactivity) and more sensitivity (i.e., affinity)* than anti-IgE binding antibodies." Frank at col. 1, lines 36-41 (emphasis added). Thus, Frank teaches that the benefit of using an FcεR is increased affinity and decreased cross-reactivity compared using an anti-IgE antibody. Based on this teaching, one of skill in the art would have been motivated to use a reagent with a high affinity for IgE.

In contrast, the rejected claims recite the use of CD23, the low affinity receptor for IgE. Based on Frank's teaching and the Office's rationale, relying on the alleged benefits of using a high affinity reagent, one of ordinary skill in the art would not have been motivated to choose the low affinity receptor. Indeed, Frank is silent about the usefulness of the low affinity receptor in an assay for analyzing the content of IgE in a liquid sample. In sum, Frank teaches away from using CD23, and thus teaches away from the claimed invention.

Regarding Jardieu, the Office continues to assert that the normal (non-variant) IgE antibody of Jardieu parallels the ligand recited in the rejected claims. *See* the Office Action at page 8 (Response to Arguments). This interpretation, however, does not accurately describe Jardieu's assay. Jardieu appears to use the biotinylated non-variant IgE as a reagent to indirectly determine the impact of making changes in IgE

antibody structure on binding to IgE receptors and/or to the anti-IgE MaE11 antibody. Specifically, the biotinylated non-variant IgE binds to the anti-IgE MaE11 antibody. Jardieu does not suggest that the biotinylated non-variant IgE binds to the variant IgE. The anti-IgE MaE11 antibody, itself, is an ***IgG*** antibody. Because the anti-IgE MaE11 antibody is of the IgG isotype, it would not bind to the Fcε receptor, which binds to IgE antibodies.

Additionally, as Applicants previously explained, the biotinylated non-variant IgE is not part of Jardieu's "sample." *See* Amendment filed March 27, 2008, at pages 15 and 16. Instead, Jardieu's sample includes the variant IgE antibodies. For example, Jardieu states that "[i]n a separate assay plate the samples and reference murine MaE11 antibody were titered . . . and an equal volume of 10 ng/ml biotinylated IgE at 10 ng/ml was added," clearly indicating that the biotinylated IgE is added to the sample, as opposed to being part of the sample. Col. 42, lines 8-12. Thus, Jardieu does not teach or suggest using the low affinity Fcε receptor to detect and/or quantify IgE that is bound to a ligand.

Regarding claim 15, although the Office contends that "Jardieu teaches that FCEH (FceRI) and FcERII (CD23)-specific, differential binding polypeptides are useful for diagnostics and therapeutics" and a "method of identifying immunoglobulin analogues that bind FCEH (FceRI) but not FCEL (FceRII- CD23)," these statements do not remedy the Office's mischaracterization of Jardieu's assay. In addition, these statements do not teach or suggest "using CD23 alone to obtain a first measurement and using FcεRI alone to obtain a second measurement, and using both the first and the second measurement as a basis for evaluating the immunological status of the

subject," as recited in claim 15. Accordingly, these statements have no bearing on claim 15. Moreover, as noted above, Frank teaches away from the use of a low affinity receptor in such an assay.

In sum, it would not have been obvious to replace Johansen's anti-IgE antibody with CD23 based on the combined teachings of Johansen, Jardieu, and Frank. Likewise, the combination of these references would not have rendered claims 1-5, 8-16, and 21-23 obvious. Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103 over Johansen, Jardieu, Frank, and Arnold

Claims 6 and 17-20 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Johansen in view of Jardieu and Frank, and in further view of U.S. Patent 6,004,745 ("Arnold"). Office Action at page 7. The Office uses Johansen, Jardieu, and Frank as discussed above. Recognizing that those references "fail to teach adding label after a first separation step and a second separation to separate the non-complexed labels," the Office alleges that Arnold teaches two separation steps in a sandwich assay. *Id.* at pages 7-8. According to the Office, it would have been obvious to add the label molecule after a first separation step and then separate the non-complexed labels as discussed in Arnold using the reagents in the method of Johansen as modified by Jardieu and Frank.

Applicants respectfully disagree. The shortcomings, described above, in the combination of Johansen, Jardieu, and Frank are not remedied by Arnold. Specifically, like those documents, Arnold does not teach using CD23 in an assay to detect and/or quantify IgE in a liquid sample. Thus, the combination of Johansen, Jardieu, Frank, and

Arnold would not have rendered claims 6 and 17-20 obvious. Applicants respectfully request that the Office withdraw this rejection.

Conclusions

In view of the foregoing remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of claims 1-6 and 8-23.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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